REMARKS

This reply supplements the remarks which were filed on November 24, 2009 and the amendment filed with the RCE in this matter on November 16, 2009.

I. Obviousness Rejection under 35 U.S.C. § 103(a)

In the previous office action claims 11-14, 16, 17, 19-31 and 47-52 were rejected under 35 U.S.C. § 103(a) as being obvious in view Bartlett et al. and Herrick-Davis et al. (*European Journal of Pharmacology*, 162:365-369, 1989).

As discussed in the remarks filed November 24, 2009, the specification of the present application explains that while certain A1 adenosine receptor agonists have been found have analgesic activity and certain A2 adenosine receptor agonists have been found to have anti-inflammatory activity, A1 receptor agonists cause bradycardia and A2A adenine receptor agonists cause vasodilatation leading to hypotension and tachycardia. For these reasons, adenosine receptor agonists were commonly considered to have limited usefulness in treatment of pain. As the specification also explains, Applicant surprisingly found that spongosine was "effective in inhibiting pain perception in mammals suffering from neuropathic and inflammatory pain even when administered at doses expected to give concentrations well below those known to activate adenosine receptors."

The attached Declaration of Peter Richardson, Ph.D., under 35 U.S.C. §1.132 presents data demonstrating that spongosine can effectively reduce pain when administered at a dosage that results in a plasma concentration that is far lower than that which would be expected to be required to activate the A1 and A2A adenosine receptors.

In his Declaration, Dr. Richardson states that he supervised a study which found that spongosine can reduce inflammatory and neuropathic pain in animals at a dose of 0.4 mg/kg pain and a study which found that spongosine can reduce diabetic neuropathic pain in humans at a dose of 0.1mg/kg. Dr. Richardson goes on to state that the dosages used result in a peak maximum plasma concentration of about 0.2 micromolar, an order of magnitude below the Kd for spongosine at the A2A adenosine receptor (about 2.0 micromolar). As Dr. Richardson

explains, one would expect that at a plasma concentration so far below the Kd of spongosine for the A1 and A2A adenosine receptor, spongosine would not activate either receptor and thus would not have an analgesic effect.

In his Declaration, Dr. Richardson explains that it appears that in certain tissues, such as epithelia; tissue damaged by physical, chemical or biological trauma; and tissues undergoing an inflammatory response, the pH is lower than that of other tissues. This lower pH alters the binding affinity of spongosine for adenosine receptors such that spongosine is selective for the A2A adenosine receptor in such tissues. This allows the unexpected alleviation of pain and inflammation by spongosine at a plasma concentration that is too low to activate A1 and A2A adenosine receptors in other tissues thereby avoiding such negative side-effects as bradycardia and hypotension respectively.

As is evident from the Declaration of Peter Richardson Under 35 U.S.C. §1.132, spongosine can unexpectedly relieve pain at dosages that are far below that which would be expected to be needed to activate the adenosine A2A receptor. In addition, spongosine can relieve pain without causing dangerous bradycardia and hypotension. These results are unexpected in view of the prior art teachings, e.g., in Bartlett et al., that spongosine causes bradycardia and hypotension.

In view of the forgoing, Applicant respectfully requests that the rejections under 35 U.S.C. §103 be reconsidered and withdrawn.

II. Conclusion

For the reasons set forth above, Applicant submits that the claims are in condition for allowance. Reconsideration and withdrawal of the Examiner's objections and rejections are hereby requested. Allowance of the claims is earnestly solicited.

In the event that a telephone conversation could expedite the prosecution of this application, the Examiner is requested to call the undersigned at 617.521.7041.

No fee is believed to be due. If, however, there are any charges or credits, please apply them to Deposit Account No. 06-1050 referencing Attorney Docket No. 13425-0170US1.

Respectfully submitted,

Date:22 December 2009

/Anita L. Meiklejohn/
Anita L. Meiklejohn, Ph.D.

Customer No. 26161
Fish & Richardson P.C.
Telephone: (650) 839-5070
Facsimile: (650) 839-5071